DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/14/2009 has been entered.

Claims Status

Claims 7-12, 14-16, and 18 are pending. Claims 9, 10, 14 and 15 are withdrawn from further consideration as being drawn to a nonelected invention, there being no allowable generic or linking claim for the reasons of record (see Office Action mailed 09/17/2007). Claims 7, 8, 11, 12, 16, and 18 are under examination insofar as they are directed to SEQ ID NO:23.

Specification – objection withdrawn

The objection to the specification for containing an embedded hyperlink is withdrawn. The amendment to the specification filed 09/14/2009 has obviated the objection.

Objection to the Specification and Drawings

(Sequence Compliance)

This application contains sequence disclosures that are encompassed by the definitions

for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant is requested to return a copy of the attached Notice to Comply with the response. To be considered fully responsive, any reply to this action must address these deficiencies, as this requirement will not be held in abeyance.

Claim Objections

The claims are objected to because of the following informalities.

The claims commence on a separate page and appear after the detailed description of the invention, but each claim is not presented as an object of a sentence starting with "We claim,", or "The invention claimed is," as per MPEP 608.01(m). Appropriate correction is required.

Claims 12 and 16 are to "a therapeutic agent for hepatitis C". Because the invention appears to be directed to siRNAs that are effective for inhibiting hepatitis C (HCV) replication or inhibiting expression of HCV RNA and that are useful for treating HCV infection, the claims would more appropriately reflect the invention by stating "a therapeutic agent for treating hepatitis C infection" or "an agent for inhibiting hepatitis C replication" or the like.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 7, 8, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir, et al. 2002 (Methods, v.26:199-213).

The claims are to an siRNA having a nucleotide sequence shown in SEQ ID NO:23 or to an siRNA having a nucleotide sequence which hybridizes under stringent conditions with an RNA region of HCV having a sequence complementary to a nucleotide sequence shown in SEQ ID NO:23. The phrase "a nucleotide sequence" is any sequence of nucleotides from as few as 2 to as many as 20 nucleotides. This is distinct from the phrase "the nucleotide sequence", which requires the entirety of SEQ ID NO:23. SEQ ID NO:23 is 5'- gucucguagaccgugcauca-3', which comprises the sequence, "CU".

Elbashir, et al. teach the siRNA duplex, GL2 (Figure 4B on page 205), which comprises the sequence "CU". This "CU" sequence would hybridize under stringent conditions with an RNA region of HCV having a sequence complementary to the sequence, "CU". Therefore, Elbashir, et al. anticipates the instant claims.

Claims 7, 8, 11, and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Yu, et al. (2002, PNAS, v.99:6047-52, of record) ("Yu").

The claims are to an siRNA having a nucleotide sequence shown in SEQ ID NO:23 or to an siRNA having a nucleotide sequence which hybridizes under stringent conditions with an RNA region of HCV having a sequence complementary to a nucleotide sequence shown in SEQ ID NO:23 and to vectors comprising the siRNAs. The phrase "a nucleotide sequence" is any sequence of nucleotides from as few as 2 to as many as 20 nucleotides. This is distinct from the phrase "the nucleotide sequence", which requires the entirety of SEQ ID NO:23. SEQ ID NO:23 is 5'- gucucguagaccgugcauca-3', which comprises the sequence, "CU".

Yu teaches expression plasmids (vectors) comprising the siRNAs shown in Figure 4A (page 6048, last paragraph; Figure 4A). The siRNAs comprise the sequence, "CU". Therefore, Yu anticipates the instant claims.

Claims 7, 8, 11, 12, 16, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Jadhav, et al. (U.S. Patent Application Publication 2005/0209180) ("Jadhav").

The claims are to an siRNA having a nucleotide sequence shown in SEQ ID NO:23 or to an siRNA having a nucleotide sequence which hybridizes under stringent conditions with an RNA region of HCV having a sequence complementary to a nucleotide sequence shown in SEQ ID NO:23 and to vectors comprising the siRNAs. The phrase "a nucleotide sequence" is any sequence of nucleotides from as few as 2 to as many as 20 nucleotides. This is distinct from the phrase "the nucleotide sequence", which requires the entirety of SEQ ID NO:23. Claims 12 and 16 are directed to a therapeutic agent for hepatitis C wherein the active ingredient is the siRNA of claim 7. Absent evidence to the contrary, an siRNA meeting the structural limitations of claim 7 is presumed to perform as a therapeutic agent for hepatitis C.

Jadhav teaches siRNAs targeting HCV for the treatment of HCV-related diseases and conditions (page 1, paragraph 2; page 3, paragraph 14). Jadhav teaches an siRNA comprising a sense strand having SEQ ID NO:298 and an antisense strand having SEQ ID NO:994. This siRNA comprises 19 nucleotides of the instantly claimed SEQ ID NO:23 as shown (Table II on page 82).

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SEQ ID NO:23              5′-gucucguagaccgugcauca - 3′

Jadhav SEQ ID NO:298      5′-gucucguagaccgugcacc -3′
                             ||||||||||||||||||
Jadhav SEQ ID NO:994      3′-cagagcaucuggcacgugg - 5′
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The invention of Jadhav also encompasses expression vectors comprising the HCV siRNAs, including viral vectors that can be used to deliver siRNAs to a subject (page 12, paragraph 73; pages 32-33, paragraph 242). Thus, Jadhav clearly anticipates the instant claims.

Claim Rejections - 35 USC § 103-maintained

Claims 7, 8, 11, 12, 16, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seki, *et al.* (1994, CA2104649, of record)("Seki"), Bass (2001, Nature v.411:428-429, of record)("Bass"), and Yu, et al. (2002, PNAS, v.99:6047-52, of record)("Yu"). This rejection is maintained for the reasons of record and is presented herein for convenience.

The claims are to an siRNA having a nucleotide sequence shown in SEQ ID NO:23 or to an siRNA having a nucleotide sequence which hybridizes under stringent conditions with an RNA region of HCV having a sequence complementary to a nucleotide sequence shown in SEQ ID NO:23 and to vectors comprising the siRNAs. The phrase "a nucleotide sequence" is any

sequence of nucleotides from as few as 2 to as many as 20 nucleotides. Claims 12 and 16 are directed to a therapeutic agent for hepatitis C wherein the active ingredient is the siRNA of claim 7. Absent evidence to the contrary, an siRNA meeting the structural limitations of claim 7 is presumed to perform as a therapeutic agent for hepatitis C.

Seki teaches an antisense nucleotide targeting HCV and complementary to SEQ ID NO:23 and that is 20 nucleotides in length. Seki discloses antisense oligonucleotides useful as antiviral agents (see abstract) and particularly discloses SEQ ID NO:83, which is complementary to nucleotides 2-20 of the instant SEQ ID NO:23 (pages 32-35). Seki does not teach siRNAs. Seki does not teach siRNAs in vectors.

Bass teaches on page 429, first column, that RNA interference is a routinely used gene silencing technique that has proven to be more robust than antisense techniques by working more often, decreasing expression to lower levels than antisense oligonucleotides, and working at concentrations several orders of magnitude below the concentrations typically used in antisense experiments.

Yu teaches that siRNAs can be expressed from a vector and that synthesis of siRNAs from an expression vector is an economical alternative to chemical synthesis and that vector-expressed siRNAs may be more practical for *in vivo* use of siRNAs, such as in intact animals and for gene therapy (abstract; p.6051, first paragraph of "Discussion"; page 6052, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of invention to make an siRNA (double-stranded RNA) targeting the region of HCV corresponding to SEQ ID NO:23 for the purpose of reducing HCV expression and to express the siRNA from a vector. Seki teaches antisense oligonucleotides that target a nucleotide sequence of the instant SEQ ID

NO:23. Bass provides a motivation to make a double-stranded RNA (siRNAs) instead of an antisense oligonucleotide by teaching that RNA interference is more robust than antisense techniques by decreasing expression to lower levels and working at much lower concentrations than antisense. Based on the motivation provided by Bass to use double-stranded RNA instead of antisense compounds to down-regulate target gene expression, one of ordinary skill in the art would recognize that targeting HCV with an siRNA corresponding to SEQ ID NO:23 would be more effective agent than targeting HCV with the antisense taught by Seki. One of ordinary skill in the art would have had a reasonable expectation of success in making and using an siRNA to reduce HCV expression because Bass teaches RNAi using dsRNA is a more specific and more potent method than antisense. Yu provides a reason to express siRNAs from vectors be teaching that such expression is more economical than chemical siRNA synthesis and may be more practical than using chemically-synthesized siRNAs for *in vivo* applications. Thus, the invention of claims 7, 8, 11, 12, 16, and 18 would have been obvious, as a whole, at the time of filing of the instant application.

Response to arguments

Applicant argues that the mechanism of siRNA-mediated gene silencing as claimed is completely different and irrelevant to the mechanism of antisense DNA-mediated gene silencing as taught by Seki (page 6 of Applicant's 09/14/2009 response). Applicant also argues that the Bass reference does not mention that an siRNA having a nucleotide sequence complementary to an antisense DNA is more effective than the antisense DNA. Applicant then concludes that a person of ordinary skill in the art would not expect that an siRNA having a nucleotide sequence complementary to a known antisense DNA is more effective than the antisense DNA. These

arguments have been considered but are not persuasive. Although siRNA-mediated gene silencing and antisense DNA-mediated gene silencing operate by distinct mechanisms, both result in and are used for the same purpose, to inhibit target gene expression. One of skill in the art seeking to inhibit HCV expression, as taught by Seki, would recognize that such inhibition could readily be accomplished not only with antisense oligonucleotides as taught by Seki, but also by the more robust method of RNA interference (siRNA-mediated gene silencing). Provided the effective antisense DNA sequences of the Seki reference, one of skill in the art would recognize such sequences as a reasonable starting point for the design of siRNAs to inhibit HCV. One of skill in the art would know that RNAi and antisense-mediated gene silencing operate by different molecular mechanisms, but would also reasonably expect antisense oligonucleotides and siRNAs targeting the same RNA to effectively silence the target.

Applicant further appears to argue that siRNAs targeting the same site as known antisense DNAs are not always effective as a substitute for the antisense DNA. Applicant also argues that siRNAs having nucleotide sequences complementary to known antisense DNAs are not always as effective as the instantly claimed siRNA having SEQ ID NO:23 (third paragraph on page 7 of 09/14/2009 response). This is not persuasive. Varying degrees of silencing by antisense DNA and by siRNAs is expected by those of skill in the art. This does not preclude the reasonable expectation by one of skill in the art that an siRNA targeting the same or similar sequence as an effective antisense DNA would be likely to inhibit gene expression to some degree. Furthermore, provided the teachings of Bass, one of skill in the art would reasonably expect at least the same degree of silencing with an siRNA as with an antisense DNA.

Finally, Applicant submits that neither Seki, Bass, nor Yu teach or suggest an siRNA having a nucleotide sequence shown in SEQ ID NO:23 as recited in claims 9 and 18 of the present invention. This is not persuasive for the aforementioned reasons.

Double Patenting

Claims 11 and 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-18, 25 and 26 of copending Application No. 10/567168 in view of Jadhav, et al. (U.S. Patent Application Publication 2005/0209180) ("Jadhav").

This is a provisional obviousness-type double patenting rejection.

The instant claims are to a vector comprising an HCV-targeted siRNA molecule having a sequence of SEQ ID NO:23.

The claims of Application No. 10/567168 are to a dumbbell-shaped DNA vector encoding an siRNA targeting HCV. The application does not teach a vector comprising an siRNA having a sequence of the instant SEQ ID NO:23.

Jadhav teaches siRNAs targeting HCV for the treatment of HCV-related diseases and conditions (page 1, paragraph 2; page 3, paragraph 14). Jadhav teaches an siRNA comprising a sense strand having SEQ ID NO:298 and an antisense strand having SEQ ID NO:994. This siRNA comprises 19 nucleotides of the instantly claimed SEQ ID NO:23 as shown in Table II on page 82. Jadhav teaches that one embodiment of the invention is an expression vector comprising the HCV siRNAs (page 12, paragraph 73).

It would have been obvious to make a dumbbell-shaped DNA vector comprising an siRNA having the instant SEQ ID NO:23 because Application No. 10/567168 teaches such vectors for expressing HCV-targeted siRNAs and Jadhav teaches the instantly claimed SEQ ID NO: 23 as an HCV-targeted siRNA that can be expressed from a vector. One of skill in the art would clearly recognize that the siRNAs of Jadhav could be expressed from the dumbbell-shaped DNA vectors of Application No. 10/567168 with a reasonable expectation of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Pitrak/
Examiner, Art Unit 1635